Remarks

The Invention

The present invention provides reagents and methods for quantitating hTERT mRNA which provide for more accurate estimates of telomerase activity and also are useful in the diagnosis of cancers. The present invention provides an accurate and reproducible measure of telomerase activity by selectively measuring mRNA that encodes an active hTERT protein.

Status of the Claims

Claims 1-27 are pending.

Claims 1-27 stand rejected.

Amendments to the Claims

Applicants have amended the claims to focus on a particular commercial embodiment. The independent method claim, Claim 1, has been amended to incorporate the limitations of dependent Claim 4. Claim 6 has been amended to correct claim dependency, and Claims 2, 4, 9, 11, 22, and 24 have been cancelled, in view of the amendment to Claim 1.

Claims 8, 10, 12, 13, and 14, have been amended for clarity.

The amendments to the claims do not introduce new matter. Applicants request entry of the amendments into the record.

The Rejection of Claims 8-14 and 21-27 under 35 U.S.C. §112, second paragraph

Claims 8-14 and 21-27 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants traverse for the reasons set forth below.

Claims 8-14:

Claims 8-14 are drawn to a method for quantitating telomerase activity in a human sample based on the results obtained quantitating hTERT mRNA in the sample using the methods of claimed in Claims 1-7. Examiner rejected Claims 8-14 as indefinite because "the method does not provide how to quantitate telomerase activity using the

hTERT mRNA in a sample." (Office action, §3A). Applicants respectfully point out that this rejection is improper.

It is not a function of the claims to specify how each step is carried out. This is a function of the specification, as set forth in 35 U.S.C. §112, first paragraph ("The specification shall contain a written description of the invention, and the manner of and process of making and using it, ..."). The function of the claims, as set forth in 35 U.S.C. §112, second paragraph, is to point out and distinctly claim the subject matter. This requirement is met by Claims 8-14, which recite as step (b) the step of "quantitating telomerase activity in said sample from the result obtained in step (a)." The mere fact that step (b) is described in generic terms does not make it indefinite. The specification teaches how to carry out step (b). For example, a preferred method of carrying out the step "quantitating telomerase activity in said sample from the result obtained in step (a)" is described in Example 5.

Examiner also suggested that the phrase "determining the telomerase activity," recited in step (b) of each claim, is unclear. Applicants have amended step (b) in Claims 8, 10, 12, 13, and 14 (Claims 9 and 11 are cancelled) to clarify that this step refers to quantitating telomerase activity.

Claims 21-27:

Claims 21-27 are drawn to a method for identifying the presence of cancer cells in a human sample based on the results obtained quantitating hTERT mRNA in the sample using the methods of claimed in Claims 1-7. Examiner rejected Claims 21-27 as indefinite because the method does not provide how to identify cancer cells by using the hTERT mRNA quantitation. The rejection is analogous to the rejection of Claims 8-14, discussed above, and, again, Applicants respectfully point out that this rejection is improper.

It is not a function of the claims to specify how each step is carried out. This is a function of the specification, as set forth in 35 U.S.C. §112, first paragraph ("The specification shall contain a written description of the invention, and the manner of and process of making and using it, ..."). The function of the claims, as set forth in 35 U.S.C. §112, second paragraph, is to point out and distinctly claim the subject matter. This

requirement is met by Claims 21-27, which recite as step (b) the step of "identifying if cancerous cells are present in said sample from the quantitative result obtained in step (a)," The mere fact that step (b) is described in generic terms does not make it indefinite. The specification teaches how to carry out step (b). For example, a preferred method of carrying out the step of "identifying if cancerous cells are present in said sample from the quantitative result obtained in step (a)" is described in Example 7 (see, in particular, page 39, lines 13-21).

Applicants respectfully request reconsideration and withdrawal of the rejections of Claims 8-14 and 21-27 under 35 U.S.C. §112, second paragraph, view of the amendments and remarks presented herein.

The Rejections under 35 U.S.C. §103

The Office action dated February 28, 2001, contained 11 closely related, but separately stated, rejections under 35 U.S.C. §103. Applicants traverse all rejections for the reasons set forth, below. To avoid redundancy in the response, Applicants first discuss the amended claims, the cited art, and the rejections in general. Applicants then discuss the separately stated rejections in view of the general remarks.

The Claims

Claims 1, 3, and 5-7 are drawn to methods of quantitating hTERT mRNA using particular primers. The particular primers used, which are a critical aspect of the claims, enable a significantly improved quantitation of hTERT mRNA.

Claims 8, 10, and 12-14 are drawn to methods of quantitating telomerase activity which involve (step (a)) quantitating hTERT mRNA according to the methods of Claims 1, 3, and 5-7, respectively, then (step (b)) quantitating the telomerase activity from the results of step (a).

Claims 21, 23, and 25-27 are drawn to methods of diagnosing the presence of cancer cells, which involve (step(a)) quantitating hTERT mRNA according to the methods of Claims 1, 3, and 5-7, respectively, then (step (b)) identifying the presence of cancer cells from the results of step (a).

Claims 15 and 16 are drawn to particular primers used in the methods, which enable a significantly improved quantitation of hTERT mRNA.

Claims 17-20 are drawn to kits containing the primers of Claims 15 and 16, and, in Claims 19 and 20, a particular probe for use in detecting the product amplified using the recited primers.

Applicants point out that the particular primers of the invention are a critical aspect of all the claims, as amended. These primers enable a significantly improved quantitation of hTERT mRNA, which improves the accuracy of an estimate of telomerase activity based on the level of hTERT mRNA and also improves the ability to diagnose the presence of cancer cells based on the level of hTERT mRNA.

The Cited References

The 11 rejections under 35 U.S.C. §103 were based on various combinations of the following 8 references. To avoid repetition in the discussion of the rejections, Applicants first discuss the teachings of the references.

1. Kilian et al., 1997, Hum. Mol. Gen. 6(12): 2011-2019 ("Kilian")

Kilian describes the hTERT gene (designated therein hTCS1) and the presence of splice variants of the expressed mRNA. To survey for splice variants, Kilian used a variety of primers throughout the gene. Kilian suggests that the altered relative expression levels of the major transcripts might be involved in regulations of this gene (page 2017, column 1, penultimate paragraph). Kilian fails to teach or suggest methods of quantitating hTERT mRNA and fails to teach or suggest the claimed primers.

2. Hudkins et al., U.S. Patent No. 5,475,110 ("Hudkins")

Hudkins was cited by Examiner as teaching mRNA quantitation. Hudkins relates to an unrelated field(fused pyrrolocarbazoles) and is silent about hTERT mRNA and primers for the amplification of hTERT mRNA.

3. Nakamura et al., GenBank accession number AF015950 ("Nakamura")

Nakamura provides the nucleic acid sequence of the hTERT gene coding region. Applicants note that this reference is cited in the specification and provided as SEQ ID NO: 1. Nakamura fails to teach or suggest the claimed methods or primers.

4. Nakamura et al., 1997, Science 277:955-959 ("Nakamura-1")

Nakamura-1 describes the isolation of the hTERT gene and comparisons of the human gene with homologous genes in other organisms. Nakamura-1 compared the relative abundance of hTERT mRNA in telomerase-negative and telomerase positive cell lines and concluded that the steady state level of hTERT mRNA was higher in immortal cell lines with active telomerase (page 957, middle column, and Figure 3). Nakamura-1 does not discuss mRNA splicing or its effect on the accuracy of estimating telomerase activity from hTERT mRNA levels, and fails to teach or suggest the claimed methods and primers.

5. Hisatomi et al., 1999, Int. J. Oncology 14: 727-732 ("Hisatomi")

Hisatomi describes an investigation of the relationship between the hTERT mRNA levels and telomerase activity in hepatocellular carcinoma (HCC). Hisatomi is discussed in detail, below, in the section relating to the factual evidence demonstrating the unexpected advantages of the claimed invention.

6. Meyerson et al., 1997, Cell 90:785-795 ("Meyerson")

Meyerson described the cloning of the gene encoding the catalytic subunit of telomerase (designated therein *hEST2*) and report that it is expressed at high levels in primary tumors, cancer cell lines, and telomerase-positive tissues, but is undetectable in telomerase-negative cell lines and differentiated telomerase-negative tissues. They report that, although they found a general correlation between *hEST2* mRNA levels and telomerase activity, these two measures where not present in a constant, predictable ratio. Consequently, Meyerson et al. speculated that other mechanisms besides the modulation of mRNA levels may be important in the regulation of telomerase activity. Meyerson does not discuss mRNA splicing or its effect on the accuracy of estimating telomerase

activity from hTERT mRNA levels, and fails to teach or suggest the claimed methods and primers.

7. Nakamura et al., 1999, Molecular Carcinogenesis 26:312-320 ("Nakamura-2")

Nakamura-2 examined telomerase activity in gastrointestinal tissues using a version of the TRAP assay, and also looked at hTERT mRNA levels. Nakamura-2 fails to teach or suggest the claimed methods and primers.

Applicants believe that the conclusions drawn by Nakamura-2 are not supported by the results reported, and that this would be clear to one of skill in the art. In particular, Applicants believe that Nakamura-2 clearly mischaracterized the RT/PCR assay used for the measurements of hTERT mRNA in at least two respects and, as a result, the reported correlation results are not valid. First, although Nakamura-2 reported that the RT/PCR used did not amplify the β-deletion mRNA transcripts (see page 314, column 1, last sentence), this is not plausible in view of the description of the assay[1]. The primers used clearly should amplify the β-deletion mRNA transcripts, and the presence of β-deletion mRNA transcripts could render estimates of the correlation between mRNA transcripts and telomerase activity unreliable. This is particularly true given that splice variants account for a significant fraction of total hTERT transcripts, and that the deletion

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[1] Nakamura amplified hTERT mRNA using primers U1513 and L1982, whose sequences are provided at page 314, column 1. By inspection, Applicants have determined that these primers hybridize to nucleotides 2175-298 and 2644-2667 of the sequence provided in the specification at pages 8-10. For Examiner's convenience, the relevant portions of the hTERT sequence are shown below with the positions of the primers indicated.

```
2161 gccgcctgag ctgtactttg tcaaggtgga tgtgacgggc gcgtacgaca ccatccccca
                5' |-----U1513-------------| 3'

2641 gctcctgcgt ttggtggatg atttcttgtt ggtgacacct cacctcaccc acgcgaaaac
       ||||||| |||||||||| |||||||
     3'ggacgca aaccacctac taaagaa 5'
```

These primers hybridize to regions which correspond to the exon 5/6 junction and to exon 10 (see the specification at page 10) and, therefore, would amplify a region spanning the β deletion (i.e., exons 7 and 8). Although Nakamura suggests that these primers did not amplify the β-deletion mRNA transcripts (see page 314, column 1, last sentence), Applicants believe that it would be obvious to one of ordinary skill in the art that this statement has no basis and is incorrect, based on the position of the primers.

transcript, being shorter, typically would be preferentially amplified in an RT/PCR, which would make detecting a positive correlation even more difficult. Second, although Nakamura-2 describes the results of the RT/PCR assay as a quantitative measurement of hTERT mRNA, Nakamura states-2 that both the RT/PCR and the image analysis of gel fluorescence upon which the supposed quantitative result are based were not quantitative (page 316, column 2). For these reasons, Applicants believe that one of ordinary skill in the art would conclude that the results reported in Nakamura-2 do not support any conclusions about a quantitative correlation.

8. Stratagene Catalog

Stratagene Catalog was cited as showing that reagents sold commercially can be packaged in kit form. The catalog does not relate to the claimed subject matter.

The Claimed Primers Are Not Obvious

As Applicants pointed out, above, the particular primers are a critical aspect of all the claims. These particular primers enable a significantly improved quantitation of hTERT mRNA, which improves the accuracy of an estimate of telomerase activity, and which also improves the ability to diagnose the presence of cancer cells.

In rejecting claims that recite particular primer sequences, Examiner suggested that the primers of the claimed invention are merely obvious variants of those described in the cited references. In particular, Examiner stated:

> Since the claimed primers (1) simply represent structural and functional homologues of the full length disclosed hTERT sequence (2) concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in absence of secondary considerations.

Office action, page 6, lines 5-9. (numbering and emphasis added). Examiner further stated:

> Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are merely function equivalents of the primers provided in the art for amplifying the hTERT gene.

Office action, page 6, lines 13-16.

Applicants respectfully disagree and assert that the rejection, as stated, is improper for at least the following reasons: (1) the particular primers are not structural and functional homologues of the full length hTERT sequence; (2) Examiner based the rejection on an improper "obvious to try" standard; and (3) Examiner improperly ignored the unexpected benefits of the claimed primers that are described in the specification. Applicants discuss each of these points, below.

(1) The claimed primers are NOT structural and functional homologues of the full length disclosed hTERT sequence.

Examiner suggested that the particular primers are obvious in view of the hTERT gene sequence because they "simply represent structural and functional homologues of the full length disclosed hTERT sequence...." The MPEP summarizes when a rejection based on structural homology is appropriate:

> A *prima facie* case of obviousness may be made when chemical compounds have a very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties"

(MPEP 2144.09, emphasis added, cites omitted). However, in the present case, neither structural similarity nor similar utilities are present. Thus, this rejection cannot be maintained (MPEP 2144.09).

Using the primer of Claim 15, SYC1097, as an example for discussion, this primer is an oligonucleotide of length 18 having a particular sequence. In contrast, the full length hTERT sequence (SEQ ID NO: 1 at pages 8-10 of the specification) represents the sequence of a single-stranded mRNA[2] molecule comprising 3961 nucleotides. The sequence of the hTERT mRNA does not even contain the sequence of primer SYC1097 as a subsequence, but rather contains the reverse complement of SYC1097 as a subsequence. As chemical compounds, these two molecules are vastly different and possess vastly different utilities. For example, the full-length hTERT mRNA cannot be

[2] SEQ ID NO: 1 also is a representation of the coding portions of a much larger molecule of double-stranded DNA, which comprises both the exons and introns of the hTERT gene, and which itself is actually a region within a chromosome.

used to amplify a target sequence within the full-length hTERT mRNA, and primer SYC1097 does not encode the hTERT protein. The presumption of obviousness based on structural similarity is overcome where there is no reasonable expectation of similar properties (MPEP 2144.09).

Applicants further maintain that two primers having different nucleotide sequences are not structural homologues in the chemical sense, even though both may hybridize to different regions of the same chromosome. Two primers with different sequences, viewed as chemical compounds, differ functionally in their hybridization properties, which is a critical property of primers in general, and in particular, the primers of the present methods. Again, the presumption of obviousness based on structural similarity is overcome where there is no reasonable expectation of similar properties (MPEP 2144.09).

(2) Examiner has applied an improper "obvious to try" standard.

"Obvious to try" has long been held not to constitute obviousness. (In re O'Farrel USPQ2d 1673, 1680-81). The rejection, suggesting that, having the full-length hTERT sequence, "a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties" clearly is based on an improper "obvious to try" standard. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out (In re Deuel, 34 USPQ2d 1210, 1216). The cited art does not suggest the particular claimed primers, which are a critical element in all the pending claims.

(3) Examiner improperly ignored the unexpected benefits of the claimed primers that are described in the specification.

The specification teaches that the claimed methods provide a more accurate surrogate measure of telomerase activity and, thereby, provide an improved marker for use in cancer diagnosis (page 3, lines 15-19). Examples 4 and 5 describe experiments that demonstrate the accuracy of estimating telomerase activity using the claimed methods. The accuracy is reflected in the strong statistical correlation between the level of hTERT mRNA, measured using the claimed methods, and telomerase activity ("The r^2

of over 96% indicates that using the hTERT mRNA as a predictor of telomerase activity provides an accurate measure of telomerase activity.", page 36, lines 23-26). Thus, the specification provides factual evidence of the advantages of the claimed invention. As discussed below, these experimental results, compared to the results described in closest art cited, show that the claimed invention provides unexpected benefits over the cited art.

Applicants submit that Hisatomi et al., 1999, Int. J. Oncology 14: 727-732 ("Hisatomi"), which was cited by Examiner, represents the closest art at the time of filing. (Applicants wish to emphasize that this is not a representation that Hisatomi is prior art under 35 U.S.C. $102 or §103). Histami describes an investigation of the relationship between the hTERT mRNA levels and telomerase activity in hepatocellular carcinoma (HCC), using methods that can be compared to the claimed methods. Below, Applicants compare and contrast the methods and results reported in Hisatomi with those provided in the specification.

Hisatomi looked at the statistical correlation between the level of hTERT mRNA and telomerase activity. Hisatomi used a TaqMan-based method to quantitate hTERT mRNA levels (page 728, column 1), and used a version of the TRAP assay to quantitate telomerase activity (page 728, column 2). The statistical correlation of hTERT mRNA with telomerase activity was obtained from a correlation coefficient analysis (page 728, column 2, "*statistical analysis*"). The analysis yielded a correlation coefficient, r, of 0.751 (page 730, column 2, last paragraph).

Analogously, Examples 4 and 5 of the specification describe the correlation between the level of hTERT mRNA and telomerase activity. The examples describe the use of a TaqMan-based method to quantitate hTERT mRNA (Example 4), and the use of a version of the TRAP assay to quantitate telomerase activity (Example 5). The statistical correlation of hTERT mRNA with telomerase activity was obtained from a correlation coefficient analysis (page 36, lines 22-26). Example 5 reports a squared correlation coefficient, r^2, of 0.9614, which is equivalent to r = .9805. Although the methods described in Examples 4 and 5 are analogous to those described by Hisatomi, a critical aspect of the claimed methods which distinguishes the claimed methods from those of Hisatomi is the primers used in the amplification.

Hisatomi amplified hTERT mRNA using primers BABO-F and BABO-R, whose sequences are provided at page 728, column 1. By inspection, Applicants have determined that these primers hybridize to nucleotides 1777-1790 and 1950-1970 of the sequence provided in the specification at pages 8-10 (Applicants note that the sequence provide for BABO-R is actually the sequence to which the primer binds - as a primer, the sequence provided would not hybridize to the hTERT sequence). For Examiner's convenience, the relevant portions of the hTERT sequence are shown below with the positions of the primers indicated.

```
1741 tgtcacggag accacgtttc aaaagaacag gctctttttc taccggaaga gtgtctggag
                                          |---- BABO-F ---------|

1921 cttcatcccc aagcctgacg ggctgcggcc gattgtgaac atggactacg tcgtgggagc
                                    |---- BABO-R ---------|
```

These primers hybridize to regions in exons 3 and 4, respectively, (see the specification at page 10) and, therefore, are not capable of selectively amplifying hTERT mRNA containing the β region (exons 7 and 8).

In contrast, Examples 4 and 5 were carried out using primers (SYC1118 and SYC1097) that hybridize to regions in exons 6 and 8 and selectively amplify only hTERT mRNA containing the β region. Applicants determined that the mRNA splice variants which encode an active hTERT protein can be discriminated from the predominant splice variants which encode inactive forms of the hTERT protein based on the presence the β region (Specification, page 3, lines 2-6).

The claimed methods provide an accurate and reproducible measure of telomerase activity by selectively measuring mRNA that encodes an active hTERT protein. A comparison of the results in Examples 4 and 5 to the results of Hisatomi demonstrate that quantitating hTERT mRNA using the claimed methods provides a significantly more accurate measure of telomerase activity. Whereas the methods of Hisatomi, based on primers that amplify a region from exons 3 and 4, showed only a moderate correlation between the level of hTERT mRNA and telomerase activity (correlation coefficient = 0.751), the claimed methods showed a very high correlation (correlation coefficient = 0.9805). Furthermore, as the primary distinction between the methods is the primers used, the results demonstrate that the improvement results from the primers used. The

improvement in the accuracy of estimating telomerase activity from the hTERT mRNA level using these primers also provides an improvement in the accuracy of diagnosing cancer, as the cancer diagnosis is based on the detection of an elevated level of telomerase activity.

From the above comparison, it is clear that the specification provides factual evidence that the claimed primers have unexpected benefits or properties such that they would not be equivalents to those provided in the cited art.

Below, Applicants discuss the specific rejections in view of the foregoing remarks.

The Rejection of Claims 1 and 3 under 35 U.S.C. §103

Claims 1 and 3 were rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of the Hudkins.

Applicants have amended Claim 1 (and, thus, dependent Claim 3) to incorporate the limitations of dependent Claim 4, which is equivalent to presenting Claim 4 in independent form. As the present rejection was not applied to Claim 4, Applicants believe that the present rejection is rendered moot by the amendments to the claims.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1 and 3 under 35 U.S.C. §103 in view of the amendments and remarks.

The Rejection of Claims 2, 4-7, and 15-16 under 35 U.S.C. §103

Claims 2, 4-7, and 15-16 were rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of Hudkins, and further in view of Nakamura (GenBank accession number AF015950). Applicants traverse for the reasons discussed below.

Claims 2 and 4 have been cancelled; amended Claim 1 is equivalent to Claim 4. As amended, all the pending claims contain as a critical limitation the particular primers of the invention. Applicants urge that the Claims 2, 4-7, and 15-16 are not obvious for the reason that the recited primers are not obvious, as discussed above.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 2, 4-7, and 15-16 under 35 U.S.C. §103 in view of the amendments and remarks.

The Rejection of Claim 21 under 35 U.S.C. §103

Claim 21was rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of the Hudkins, and further in view of Nakamura-1. Applicants traverse for the reasons discussed below.

Claim 21 recites carrying out the method of Claim 1, which has been amended to recite the use of the particular primers of the invention. Applicants urge that the Claim 21 is not obvious for the reason that the recited primers are not obvious, as discussed above.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claim 21 under 35 U.S.C. §103 in view of the amendments and remarks.

The Rejection of Claims 22-27 under 35 U.S.C. §103

Claims 22-27 were rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of the Hudkins, and further in view of Nakamura, and further in view of Nakamura-1. Applicants traverse for the reasons discussed below.

Claims 22 and 24 have been cancelled. Claims 23 and 25-27 depend ultimately from Claim 1, which has been amended to recite the use of the particular primers of the invention. Applicants urge that the Claims 22 and 25-27 are not obvious for the reason that the recited primers are not obvious, as discussed above.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 22-27 under 35 U.S.C. §103 in view of the amendments and remarks.

The Rejection of Claims 1, 3, 8, and 21 under 35 U.S.C. §103

Claims 1, 3, 8, and 21 were rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of the Hisatomi.

Applicants have amended Claim 1, and, thus, dependent Claims 3, 8, and 21, to incorporate the limitations of dependent Claim 4, which is equivalent to presenting Claim 4 in independent form. As the present rejection was not applied to Claim 4, Applicants believe that the present rejection is rendered moot by the amendments to the claims.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 3, 8, and 21 under 35 U.S.C. §103 in view of the amendment to the claims.

The Rejection of Claims 2, 4-7, 9-14, and 22-27 under 35 U.S.C. §103

Claims 2, 4-7, 9-14, and 22-27 were rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of the Hisatomi, and further in view of Nakamura. Applicants traverse for the reasons discussed below.

Claims 2 and 4 have been cancelled; amended Claim 1 is equivalent to Claim 4. As amended, all the pending claims contain as a critical limitation the particular primers of the invention. Applicants urge that the Claims 2, 4-7, 9-14, and 22-27 are not obvious for the reason that the recited primers are not obvious, as discussed above.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 2, 4-7, 9-14, and 22-27 under 35 U.S.C. §103 in view of the amendments and remarks.

The Rejection of Claims 1, 3, and 21 under 35 U.S.C. §103

Claims 1, 3, and 21 were rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of the Meyerson.

Applicants have amended Claim 1, and, thus, dependent Claims 3 and 21, to incorporate the limitations of dependent Claim 4, which is equivalent to presenting Claim 4 in independent form. As the present rejection was not applied to Claim 4, Applicants believe that the present rejection is rendered moot by the amendments to the claims.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 3, and 21 under 35 U.S.C. §103 in view of the amendment to the claims.

The Rejection of Claims 2, 4-7, and 22-27 under 35 U.S.C. §103

Claims 2, 4-7, and 22-27 were rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of Meyerson, and further in view of Nakamura .
Applicants traverse for the reasons discussed below.

Claims 2 and 4 have been cancelled; amended Claim 1 is equivalent to Claim 4. As amended, all the pending claims contain as a critical limitation the particular primers of the invention. Applicants urge that the Claims 2, 4-7, and 22-27 are not obvious for the reason that the recited primers are not obvious, as discussed above.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 2, 4-7, and 22-27 under 35 U.S.C. §103 in view of the amendments and remarks.

The Rejection of Claims 1, 3, and 21 under 35 U.S.C. §103(a)

Claims 1, 3, and 21 were rejected under 35 U.S.C. §103(a) as unpatentable over Kilian in view of the Nakamura-2.

Applicants have amended Claim 1, and, thus, dependent Claims 3 and 21, to incorporate the limitations of dependent Claim 4, which is equivalent to presenting Claim 4 in independent form. As the present rejection was not applied to Claim 4, Applicants believe that the present rejection is rendered moot by the amendments to the claims.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 3, and 21 under 35 U.S.C. §103(a) in view of the amendment to the claims.

The Rejection of Claims 2, 4-7, and 22-27 under 35 U.S.C. §103(a)

Claims 2, 4-7, and 22-27 were rejected under 35 U.S.C. §103(a) as unpatentable over Kilian in view of the Nakamura-2, and further in view of Nakamura. Applicants traverse for the reasons discussed below.

Claims 2 and 4 have been cancelled; amended Claim 1 is equivalent to Claim 4. As amended, all the pending claims contain as a critical limitation the particular primers of the invention. Applicants urge that the Claims 2, 4-7, and 22-27 are not obvious for the reason that the recited primers are not obvious, as discussed above.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 2, 4-7, and 22-27 under 35 U.S.C. §103(a) in view of the amendments and remarks.

The Rejection of Claims 17-20 under 35 U.S.C. §103

Claims 17-20 were rejected under 35 U.S.C. §103 as unpatentable over Kilian in view of Hudkins, and further in view of Nakamura, and further in view of Stratagene Catalog. Applicants traverse for the reasons discussed below.

Claims 17-20 are drawn to kits containing the particular primer of Claims 15 or the primer pair of Claim 16. Applicants urge that the Claims 17-29 are not obvious for the reason that the recited primers are not obvious, as discussed above.

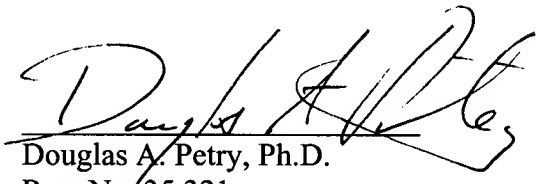
The kits of Claims 19 and 20 additionally contain specific probes which are not taught or suggested by the cited references. A kit containing nonobvious oligonucleotides is not obvious for the same reasons.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 17-20 under 35 U.S.C. §103 in view of the above remarks.

Conclusion

Applicants believe that all issues raised in the Office action dated February 28, 2001, have been addressed and that the application is now in condition for allowance. Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1 and 3 under 35 U.S.C. §103; the rejection of Claims 2, 4-7, and 15-16 under 35 U.S.C. §103; the rejection of Claim 21 under 35 U.S.C. §103; the rejection of Claims 22-27 under 35 U.S.C. §103; the rejection of Claims 1, 3, 8, and 21 under 35 U.S.C. §103; the rejection of Claims 2, 4-7, 9-14, and 22-27 under 35 U.S.C. §103; the rejection of Claims 1, 3, and 21 under 35 U.S.C. §103; the rejection of Claims 2, 4-7, and 22-27 under 35 U.S.C. §103; the Rejection of Claims 1, 3, and 21 under 35 U.S.C. §103(a); the second rejection of Claims 2, 4-7, and 22-27 under 35 U.S.C. §103(a); and the rejection of Claims 17-20 under 35 U.S.C. §103; in view of the amendments and remarks presented herein.

Respectfully submitted:



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Claim Amendments: Version with Markings to Show Changes Made

1. (amended) A method for quantitating hTERT mRNA in a human sample, wherein said method comprises:

(a) contacting RNA from said sample with amplification reagents comprising a pair of primers, wherein said pair of primers consists of a first primer that is SYC1076 (SEQ ID NO: 2) or SYC1118 (SEQ ID NO: 5)[complementary or substantially complementary to one strand of the double-stranded hTERT gene sequence that is SEQ ID NO: 1 in a region that is either upstream of exon 7 or downstream of exon 8,] and a second primer that is SYC1097 (SEQ ID NO: 4)[complementary or substantially complementary to the other strand of said hTERT gene sequence in a region within exon 8];

(b) carrying out an amplification reaction;

(c) measuring the generation of amplification products; and

(d) determining the quantity of hTERT mRNA in said sample from the results obtained in step (c).

6. (amended) A method of Claim [4]3, wherein step (c) is carried out using a probe that is complementary or substantially complementary to said amplification products.

8. (amended) A method for quantitating telomerase activity in a human sample, wherein said method comprises:

(a) quantitating hTERT mRNA in said sample using the method of Claim 1; and

(b) [determining the]quantitating telomerase activity in said sample from the result obtained in step (a).

10. (amended) A method for quantitating telomerase activity in a human sample, wherein said method comprises:

(a) quantitating hTERT mRNA in said sample using the method of Claim 3; and

(b) [determining the]quantitating telomerase activity in said sample from the result obtained in step (a).

12. (amended) A method for quantitating telomerase activity in a human sample, wherein said method comprises:

(a) quantitating hTERT mRNA in said sample using the method of Claim 5; and

(b) [determining the]quantitating telomerase activity in said sample from the result obtained in step (a).

13. (amended) A method for quantitating telomerase activity in a human sample, wherein said method comprises:

(a) quantitating hTERT mRNA in said sample using the method of Claim 6; and

(b) [determining the]quantitating telomerase activity in said sample from the result obtained in step (a).

14. (amended) A method for quantitating telomerase activity in a human sample, wherein said method comprises:

(a) quantitating hTERT mRNA in said sample using the method of Claim 7; and

(b) [determining the]quantitating telomerase activity in said sample from the result obtained in step (a).